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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,620	01/29/2007	Maria Sitges Berrondo	251989	9639

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER
CARTER, KENDRA D

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
05/12/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Chgpatent@leydig.com

Office Action Summary	Application No.	Applicant(s)	
	10/577,620	SITGES BERRONDO ET AL.	
	Examiner	Art Unit	
	KENDRA D. CARTER	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 29, 2010 has been entered.

Claims 1, 3 and 4 are pending. Claims 2 and 5-8 are cancelled.

In light of the amendments to the claims, the 35 U.S.C. 112, first paragraph rejections over claims 2 and 3 are withdrawn.

In light of the amendments to the claims, the 35 U.S.C. 112, second paragraph rejections over claims 1-3 are withdrawn.

In light of the amendments to the claims, the 35 U.S.C. 103(a) rejection over claims 1-3 is withdrawn.

In light of further consideration and the amendments to the claims the new rejections are below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claims 1, 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating hearing loss in the 4 and 8 kHz tone frequencies associated with epilepsy for an hour, does not reasonably provide enablement for completely preventing hearing loss of retro-cochlear origin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of preventing hearing loss of retro-cochlear origin comprising administering vinpocetine. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have

required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method of simultaneously preventing hearing loss of retro-cochlear origin and epileptic seizures, the method comprising prophylactically administering to a subject in need thereof vinpocetin, in a sufficient amount for simultaneously inhibiting auditory tract alterations linked to the hearing loss and seizures."

(2) The breadth of the claims:

Claim 1 embraces and reads on completely preventing hearing loss of retro-cochlear origin and simultaneously preventing epileptic seizures. The specification does not enable the prevention of hearing loss from any retro-cochler origin for any amount of time.

(3) The state of the prior art:

The state of the art regarding preventing hearing loss is very low or do not exist. Nekrassov et al. teach that vinpocetine has protective effects but does not indicate that vinpocetine completely prevent hearing loss (see page 227, column 1, section 4.1). Vinpocetine is given after the administration of AMIKACIN, not before (see page 223, column 1, section 2.1). The normal human's hearing range is from 16 Hz to 16.3 mHz (see Wikipedia, page 1, first paragraph).

Atcherson et al. (Journal of the Association of Medical Professionals with Hearing Losses, vol. 1, no. 2, Spring 2003) teach that retrocochlear hearing loss refers to hearing disorders associated with the auditory nerve to the auditory centers of the brain. Progressive neural disorders, such as multiple sclerosis, can obscure sound information being sent by the cochlea. Tumors developing on the auditory nerve can wipe out large frequency regions within the range of speech sounds, making it difficult to understand speech. Lesions of the brain whether traumatic, vascular, chemical, neoplastic, or development, can cause a variety of different auditory processing disorders (see page 3).

Temkin (Epilepsia, 2001, vol. 42, no. 4, pp. 515-524) teach that for unprovoked (epileptic) seizures, no drug has been shown to be effective, and some have had a clinically important effect ruled out (see abstract). Several animal models of epileptogenesis (the process by which a brain becomes epileptic or starts generating spontaneous seizures) exist, but we do not know which, if any, accurately reflects the process in humans. These models include kindling; status epilepticus induced by

chemicals such as picrotoxin or bicuculline; an application of alumina gel, iron compounds, or penicillin to the brain. These models have an interval between the initial insult and the development of spontaneous seizures. Although laboratory models can be very helpful in elucidating mechanisms and pointing out drugs that are likely to have an antiepileptogenic effect, one needs to have clinical trails to confirm the effect in humans. Clinical trials must overcome several problems to demonstrate antiepileptogenesis. First, a decreased seizure rate while the drug is being given may reflect antiepileptogenesis, but it also could be explained by an antiepileptic effect. This can be overcome by having the primary observation period after the drug has bee stopped. Even this is not sufficient to claim that the drug *prevents* the epileptic process. It may just have delayed it so the seizures do not occur until after the observation period is over. A long delay in the epileptogenic process still may provide clinical benefit, and certainly indicates an effect on epileptogenesis (see page 515, right column to page 516, left column). The design of future studies to evaluate antiepileptogenesis provides interesting challenges. A short treatment period improves compliance, minimizes adverse effects, minimizes cost, and minimizes the number of patients who develop seizures and ethically cannot be left taking placebo until the post-treatment evaluation period begins. However, not knowing how the process of epiliptogenesis works in humans, and hence when the treatment must be on board to spot the process, one risk stopping the drug too soon for it to be optimally effective. Conversely, long treatment periods mean that many patients would have had several seizures while taking the blinded drug and would likely have had their assigned study medication discontinued

and been given a drug that was clinically indicated. To the extent the new drug is effective, this practice will diminish the observed difference between placebo and active study drugs after the study drugs were, by protocol, to be stopped. In reality, the power to detect a truly antiepileptogenic drug may not be too badly compromised by this factor, because remote symptomatic seizures have been the most difficult to get into remission and >80% of patients in a study of PHT after traumatic brain injury had additional seizures despite being treated with therapeutic levels of PHT after the first unprovoked seizure and as clinically indicated after the second (see page 522, left column, third paragraph).

(4) The predictability or unpredictability of the art:

The predictability of completely preventing hearing loss of retro-cochlear origin for any amount of time is relatively low. Therefore, to one skilled in the art, prevention of hearing loss of any retro-cochlear origin for any amount of time is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high as evidenced by Nekrassov et al., Atcherson et al. and Temkin.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to the complete prevention of hearing loss is lacking. The specification as filed does not speak on or show any working examples any studies performed that completely prevents hearing loss. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. The specification teaches that when vinpocetin is pre-injected before the convulsing agent is administered, the animals do not have hearing loss in the 4 and 8 kHz tone frequencies for up to 1 hour (see page 8, paragraph 35; the table on page 9; and figure 2). The specification does not provide this effect in all, or a larger subset of hearing frequencies; a study in humans; nor for longer periods of time. Thus, hearing loss may occur, but not in the 4 and 8 kHz tone frequencies. As Wikipedia teaches, the normal human's hearing range is from 16 Hz to 16.3 mHz. Further, if one were to provide prevention of hearing loss of all retro-cochlear origin one would theoretically have to administer vinpocetine before the development of a lesion or tumor whether from traumatic, vascular, chemical, neoplastic or developmental in order to protect the nerve from damage. The Applicant's evidence is that vinposcetine administered before the cause of the hearing loss (i.e. an epileptic seizure) prevents the hearing loss in the 4kHZ and 8kHz tone frequencies for one hour (see figure 2). Therefore, one would have to predict when an individual or circumstances when a lesion or tumor was not present on the auditory nerve and then administer vinpocetine. The above prediction has not been demonstrated in the art. Usually, one diagnoses the lesion or tumor after

it has appeared. Additionally, since the present claims are tied to simultaneously preventing an epileptic seizure, as Temkin teaches that although laboratory models can be very helpful in elucidating mechanisms and pointing out drugs that are likely to have an antiepileptogenic effect, one needs to have clinical trails to confirm the effect in humans. Clinical trials must overcome several problems to demonstrate antiepileptogenesis. First, a decreased seizure rate while the drug is being given may reflect antiepileptogenesis, but it also could be explained by an antiepileptic effect. This can be overcome by having the primary observation period after the drug has bee stopped. Even this is not sufficient to claim that the drug *prevents* the epileptic process. It may just have delayed it so the seizures do not occur until after the observation period is over. A long delay in the epileptogenic process still may provide clinical benefit, and certainly indicates an effect on epileptogenesis (see page 515, right column to page 516, left column). Thus, prevention of all hearing loss of retro-cochlear origin for any amount of time (i.e. indefinitely) is not enabled.

(7) The quantity of experimentation necessary:

The instant claims read on the completely preventing hearing loss of any retro-cochlear origin. As discussed above the specification fails to provide any support for completely preventing hearing loss of any retro-cochlear origin. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion"

and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable. Since only the 4 and 8kHz tone frequencies were tested, one can not assume that there is no hearing loss in the other frequencies (i.e. 16 Hz to 3kHz). The tone frequencies tested does not provide a good representation of the frequencies that a normal human hears. Further humans were not tested for longer periods of time in clinical studies.

In conclusion, the applicant is enabled for treating hearing loss associated with epilepsy at 4 and 8 kHz for 1 hour, but not for completely preventing hearing loss of any retro-cochlear origin for any amount of time.

2) Claim 1, 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating epileptic seizures for up to 80 minutes comprising prophylactically administering vinpocetine, does not reasonably provide enablement for completely preventing epileptic seizures. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of preventing hearing loss of retro-cochlear origin comprising administering vinpocetine. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the

court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method of simultaneously preventing hearing loss of retro-cochlear origin and epileptic seizures, the method comprising prophylactically administering to a subject in need thereof vinpocetin, in a sufficient amount for simultaneously inhibiting auditory tract alterations linked to the hearing loss and seizures."

(2) The breadth of the claims:

Claim 1 embraces and reads on completely preventing epileptic seizures. The specification does not enable the prevention of epileptic seizures.

(3) The state of the prior art:

The state of the art regarding preventing hearing loss is very low or do not exist. Temkin (Epilepsia, 2001, vol. 42, no. 4, pp. 515-524) teach that for unprovoked

(epileptic) seizures, no drug has been shown to be effective, and some have had a clinically important effect ruled out (see abstract). Several animal models of epileptogenesis (the process by which a brain becomes epileptic or starts generating spontaneous seizures) exist, but we do not know which, if any, accurately reflects the process in humans. These models include kindling; status epilepticus induced by chemicals such as picrotoxin or bicuculline; an application of alumina gel, iron compounds, or penicillin to the brain. These models have an interval between the initial insult and the development of spontaneous seizures. Although laboratory models can be very helpful in elucidating mechanisms and pointing out drugs that are lkely to have an antiepileptogenic effect, one needs to have clinical trails to confirm the effect in humans. Clinical trials must overcome several problems to demonstrate antiepileptogenesis.. First, a decreased seizure rate while the drug is being given may reflect antiepileptogenesis, but it also could be explained by an antiepileptic effect. This can be overcome by having the primary observation period after the drug has been stopped. Even this is not sufficient to claim that the drug *prevents* the epileptic process. It may just have delayed it so the seizures do not occur until after the observation period is over. A long delay in the epileptogenic process still may provide clinical benefit, and certainly indicates an effect on epileptogenesis (see page 515, right column to page 516, left column). The design of future studies to evaluate antiepileptogenesis provides interesting challenges. A short treatment period improves compliance, minimizes adverse effects, minimizes cost, and minimizes the number of patients who develop seizures and ethically cannot be left taking placebo until the post-treatment evaluation

period begins. However, not knowing how the process of epiliptogenesis works in humans, and hence when the treatment must be on board to spot the process, one risk stopping the drug too soon for it to be optimally effective. Conversely, long treatment periods mean that many patients would have had several seizures while taking the blinded drug and would likely have had their assigned study medication discontinued and been given a drug that was clinically indicated. To the extent the new drug is effective, this practice will diminish the observed difference between placebo and active study drugs after the study drugs were, by protocol, to be stopped. In reality, the power to detect a truly antiepileptogenic drug may not be too badly compromised by this factor, because *remote symptomatic seizures have been the most difficult to get into remission and >80% of patients in a study of PHT after traumatic brain injury had additional seizures despite being treated with therapeutic levels of PHT after the first unprovoked seizure and as clinically indicated after the second* (see page 522, left column, third paragraph).

(4) The predictability or unpredictability of the art:

The predictability of completely preventing an epileptic seizure is relatively low. Therefore, to one skilled in the art, prevention of an epileptic seizure is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high as evidenced by Temkin.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to the complete prevention of hearing loss is lacking. The specification as filed does not speak on or show any working examples any studies performed that completely prevents hearing loss. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. The specification teaches that when vinpocetin is pre-injected before the convulsing agent is administered, the animals do not have convulsions for up to 80 minutes (see figures 3, 4, 6 and 7). The specification does not provide this effect for long term or withdrawal of the drug such that the patient never has a seizure. Temkin teaches that although laboratory models can be very helpful in elucidating mechanisms and pointing out drugs that are likely to have an antiepileptogenic effect, one needs to have clinical trails to confirm the effect in humans. Clinical trials must overcome several problems to demonstrate antiepileptogenesis. First, a decreased seizure rate while the drug is being given may reflect antiepileptogenesis, but it also could be explained by an antiepileptic effect. This can be overcome by having the primary observation period after the drug has been stopped. Even this is not sufficient to claim that the drug *prevents* the epileptic process. It may just have delayed it so the seizures do not occur until after the observation period is over. A long delay in the epileptogenic process still may provide clinical benefit, and certainly indicates an effect on epileptogenesis (see

page 515, right column to page 516, left column). However, not knowing how the process of epiliptogenesis works in humans, and hence when the treatment must be on board to spot the process, one risk stopping the drug too soon for it to be optimally effective.

(7) The quantity of experimentation necessary:

The instant claims read on the completely preventing epileptic seizures. As discussed above the specification fails to provide any support for completely preventing epileptic seizures. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F. 3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable. As discussed above, further testing is needed such as intensive clinical trials to validated true antiepileptogenesis.

In conclusion, the applicant is enabled for treating epileptic seizures for up to 80 minutes comprising prophylactically administering vinpocetine, but not for completely preventing an epileptic seizure.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 9:00 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KENDRA D CARTER
Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627